General

Guideline Title

Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease.

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Mar. 84 p. (Technology appraisal guidance; no. 217).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (amended). London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Aug 1. 84 p. (Technology appraisal guidance; no. 111).

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC) and the National Institute for Health and Clinical Excellence (NICE): This guidance replaces NICE technology appraisal guidance 111 issued in November 2006 (amended September 2007, August 2009).

The review and re-appraisal of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease has resulted in a change in the guidance. Specifically:

- Donepezil, galantamine and rivastigmine are now recommended as options for managing mild as well as moderate Alzheimer's disease, and
- Memantine is now recommended as an option for managing moderate Alzheimer's disease for people who cannot take acetylcholinesterase (AChE) inhibitors, and as an option for managing severe Alzheimer's disease.

Guidance

The three AChE inhibitors donepezil, galantamine, and rivastigmine are recommended as options for managing mild to moderate Alzheimer's disease under all of the conditions specified below.

Memantine is recommended as an option for managing Alzheimer's disease for people with:

- Moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors or

- Severe Alzheimer's disease

Treatment should be under the conditions specified below.

Treatment should be under the following conditions:

- Only specialists in the care of people with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of the older people) should initiate treatment. Carers' views on the patient's condition at baseline should be sought.
- Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms.
- Patients who continue on treatment should be reviewed regularly using cognitive, global, functional, and behavioural assessment. Treatment should be reviewed by an appropriate specialist team, unless there are locally agreed protocols for shared care. Carers' views on the patient's condition at follow-up should be sought.

If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles.

When using assessment scales to determine the severity of Alzheimer's disease, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the results and make any adjustments they consider appropriate. Healthcare professionals should also be mindful of the need to secure equality of access to treatment for patients from different ethnic groups, in particular those from different cultural backgrounds.

When assessing the severity of Alzheimer's disease and the need for treatment, healthcare professionals should not rely solely on cognition scores in circumstances in which it would be inappropriate to do so. These include:

- If the cognition score is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient's dementia because of the patient's learning difficulties or other disabilities (for example, sensory impairments), linguistic or other communication difficulties or level of education or
- If it is not possible to apply the tool in a language in which the patient is sufficiently fluent for it to be appropriate for assessing the severity of dementia or
- If there are other similar reasons why using a cognition score, or the score alone, would be inappropriate for assessing the severity of dementia.

In such cases healthcare professionals should determine the need for initiation or continuation of treatment by using another appropriate method of assessment.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Alzheimer's disease (AD)

Guideline Category

Assessment of Therapeutic Effectiveness

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Geriatrics

Internal Medicine

Neurology

Pharmacology

Psychiatry

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost effectiveness of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease

Target Population

Patients with Alzheimer's disease (AD)

Interventions and Practices Considered

1. Acetylcholinesterase inhibitors
    - Donepezil
    - Galantamine
    - Rivastigmine
2. Memantine
3. Consideration of physical, sensory or learning disabilities, and communication difficulties when assessing disease severity and response to treatment

Major Outcomes Considered

- Clinical effectiveness
    - Measures of severity and response to treatment
    - Behavioural symptoms
    - Mortality
    - Ability to remain independent

    - Likelihood of admission to residential/nursing care
    - Health-related quality of life (HRQL) of patients and carers
    - Adverse effects of treatment
- Cost effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Peninsula Technology Assessment Group (PenTAG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Identification of Studies

Electronic databases were searched for systematic reviews and/or meta-analyses, randomised controlled trials (RCTs) and ongoing research in November 2009 and updated in March 2010; this updated search revealed no new includable studies. Appendix 2 of the assessment report shows the databases searched and the strategies in full. These included: The Cochrane Library (2009 Issue 4, CDSR and CENTRAL), MEDLINE, MEDLINE In Process, EMBASE, PsycINFO, EconLIT, ISI Web of Science Databases: Science Citation Index, Conference Proceedings Citation Index - and Biosis, the Centre for Reviews and Dissemination (CRD) databases: National Health Service Economic Evaluation Database (NHSEED), Health Technology Assessment (HTA), and Database of Abstracts of Reviews of Effects (DARE). Where possible a controlled trials and human filter was added. As this is an update of a previous review, the searches were run in the timeframe 2004 to current. The meta-register of controlled trials and clincaltrials.gov were searched for ongoing trials. Bibliographies of included studies were searched for further relevant studies. The reference lists of the industry submissions were also scrutinised for additional studies. Due to resource limitations the search was restricted to English language papers only. All references were managed using Reference Manager (Professional Edition Version 11; Thomson ISI ResearchSoft) and Microsoft Access 2003 software.

Relevant studies were identified in two stages. Titles and abstracts returned by the search strategy were examined independently by two researchers and screened for possible inclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Two researchers examined these independently for inclusion or exclusion, and disagreements were again resolved by discussion.

Inclusion and Exclusion Criteria

Study Design

Inclusion Criteria

For the review of clinical effectiveness, only systematic reviews of RCTs and RCTs were considered. The review protocol made provision for broadening search criteria to include some observational evidence if insufficient systematic reviews or RCTs were identified; however, this proved unnecessary in view of the reasonable yield of evidence of a preferred design (see below).

Systematic reviews were used as a source for finding further RCTs and to compare with the Assessment Group's systematic review. For the purpose of this review, a systematic review was defined as one that has:

- A focused research question
- Explicit search criteria that are available to review, either in the document or on application
- Explicit inclusion/exclusion criteria, defining the population(s), intervention(s), comparator(s), and outcome(s) of interest
- A critical appraisal of included studies, including consideration of internal and external validity of the research
- A synthesis of the included evidence, whether narrative or quantitative

Exclusion Criteria

Studies were excluded if they did not match the inclusion criteria, and in particular:

- Non-randomised studies (except for adverse events [AEs])
- Animal models
- Pre-clinical and biological studies
- Narrative reviews, editorials, opinions
- Non-English language papers
- Reports published as meeting abstracts only, where insufficient methodological details were reported to allow critical appraisal of study quality

Population

Studies were included if they reported a population comprising adults with Alzheimer's disease (AD). Following the 2004 review, where trials included participants with mixed dementia, these were included where the predominant dementia was AD.

Participants in included trials were required to meet the definitions of disease severity specified in the technologies' UK marketing authorisations (Mini-mental State Examination [MMSE] 26–10 for donepezil, galantamine, and rivastigmine; MMSE 20–0 for memantine).

Interventions and Comparators

Studies were included if the technologies they assessed fulfilled the following criteria:

Interventions: The four technologies under review were considered within their UK marketing authorisations:

- Mild-to-moderately severe AD (measured by the MMSE 26–10): donepezil, galantamine, and rivastigmine
- Moderate-to-severe AD (measured by the MMSE 20–0): memantine

Comparators: For people with mild AD the comparators of interest were placebo and/or best supportive care (i.e., treatment without acetylcholinesterase inhibitors [AChEIs] and without memantine). For people with moderate AD the comparators were donepezil, galantamine, rivastigmine, memantine, and placebo and/or best supportive care (BSC) (i.e., treatment without AChEIs). For people with severe AD the comparator was treatment without memantine.

Outcomes

Studies were included if they reported data on one or more of the following outcomes:

- Measures of severity and response to treatment
- Behavioural symptoms
- Mortality
- Ability to remain independent
- Likelihood of admission to residential/nursing care
- Health-related quality of life (HRQL) of patients and carers
- AEs of treatment

See Appendix 2 of the assessment report for additional information.

Cost Effectiveness

Published Economic Evaluations

The search strategy included all those databases searched for clinical effectiveness and in addition NHSEED and Econlit. The inclusion and exclusion criteria for the systematic review of economic evaluations were identical to those for the systematic review of clinical effectiveness with the exception of the target study designs. The review targeted economic evaluations including decision model based analyses, analyses of patient-

level cost and effectiveness data alongside RCTs and observational studies, full cost-effectiveness analyses, cost–utility analyses, cost-benefit analyses, cost consequence analyses and standalone cost analyses based in the UK NHS.

The systematic review of economic evaluations identified 23 included studies, over a third of which were only published as abstracts and could not be considered in depth. Of the remainder, most addressed the costs and cost-effectiveness of either donepezil or memantine. Of these, the majority reapplied modelling approaches considered as part of the last guidance to the circumstances applying in other countries and were thus felt to add little to this update reconsidering cost-effectiveness in England and Wales.

See Appendix 2 of the assessment report for additional information.

Number of Source Documents

Clinical Effectiveness

A total of 21 studies met inclusion criteria: 17 randomised controlled trials (RCTs) and 4 systematic reviews.

Cost Effectiveness

- A total of 27 papers describing 23 studies met inclusion criteria.
- Two cost-effectiveness models were submitted by the manufacturers: 1) for donepezil and 2) memantine.
- The Assessment Group presented an independent economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Peninsula Technology Assessment Group (PenTAG) (see the "Companion Documents" field).

Clinical Effectiveness

Data Extraction Strategy

Data were extracted by one reviewer into forms in bespoke software and checked by a second reviewer. Disagreements were resolved by discussion. The items extracted can be found in the data extraction forms of included studies, which are available in Appendix 3 of the assessment report.

Critical Appraisal Strategy

Assessments of study quality were performed according to the instrument developed for the 2004 review (which was based on criteria

recommended by the National Health Service Centre for Reviews and Dissemination [NHS CRD]). The instrument is summarised in section 4.1.4.1 of the assessment report. For full details, see Appendix 5 of the 2004 review. Results were tabulated and the relevant aspects described in the data extraction forms.

Methods of Quantitative Synthesis

Where data permitted, the results of individual trials were pooled using the following methods:

- Pairwise meta-analysis. The Assessment Group used random-effects meta-analyses (DerSimonian and Laird model) only, regardless of any statistical evidence of inter-study homogeneity. Analyses were conducted using bespoke software, written in Visual Basic for Applications and applied in both Microsoft Access and Microsoft Excel.
- Pooling of multiple outcome measures. In addition to pairwise meta-analyses of treatment effect pooled on each outcome's natural scale (weighted mean difference), the Assessment Group combined outcomes in a series of broad domains – cognitive, functional, behavioural, and global – to investigate the overall characteristics of reported effectiveness evidence in each area. In order to combine studies using different outcome measures within each domain, effect sizes were expressed as a standardised mean difference.
- Meta-regression. Where there was sufficient evidence (at least five individual datapoints in a meta-analysis), study level regression ("meta-regression") was used to explore the statistical heterogeneity across studies. Three prespecified covariates were explored: population age, population sex, and baseline disease severity (as measured by Mini-Mental State Examination [MMSE]). Because of inconsistencies in the evidence-base, it was not possible to undertake multivariate analyses, so regressions were conducted solely on a univariate basis.
- Mixed treatment comparison – indirect comparison. In addition to pairwise meta-analyses, where sufficient data was available, the Assessment Group synthesised information on all technologies and their comparators simultaneously, in a mixed treatment comparison (MTC) using Bayesian Markov Chain Monte-Carlo (MCMC) sampling. The analyses were performed using WinBUGS 1.4.1; model code is reproduced in Appendix 8 of the assessment report.

See section 4 in the assessment report for more information.

Cost-Effectiveness

Systematic Review of Existing Economic Evaluations

Study Quality Assessment

The methodological quality of the economic evaluations was assessed according to internationally accepted criteria such as the City Health Economics Centre (CHEC) list questions developed by Evers and colleagues. Any studies based on decision models were assessed against the International Society for Pharmacoeconomic and Outcomes Research (ISPOR) guidelines for good practice in decision analytic modelling.

Data Extraction Strategy

For those studies which were of relevance to the current decision problem, data were extracted by one researcher into two summary tables: one to describe the study design of each economic evaluation and the other to describe the main results. (These have been merged for this report.)

Synthesis of Extracted Evidence

Narrative synthesis, supported by the data extraction tables, was used to summarise the evidence base.

See section 5 of the assessment report for more information on existing economic evaluations.

Industry Submissions

Two cost-effectiveness models were submitted by the manufacturers of donepezil and memantine and appraised.

The model for donepezil has been described as a discrete event simulation model. This is a modelling approach which theoretically could overcome a number of challenges facing the assessment of the cost-effectiveness of drug treatments for Alzheimer's disease (AD), particularly dealing with multiple interdependent outcomes. However, the model does not employ a pure discrete event simulation approach and actually incorporates elements of individual sampling alongside some cohort modelling methods. The manufacturer's conclusion is that donepezil provides benefits at reduced costs relative to best supportive care, and is thus dominant, in both mild and moderately severe AD, a conclusion which is robust to the sensitivity analyses conducted by the manufacturer. However, the review of the submitted model identified several areas where there was concern with respects to the quality of the inputted data or the validity of the model assumptions. Exploratory sensitivity analyses examining plausible alternative assumptions suggest that the cost-effectiveness could be at the margins of what would normally be considered cost-effective by NICE.

The model for memantine used a more traditional Markov approach with three states, pre full time care, full time care and death. It concludes that memantine provides benefits at reduced costs relative to best supportive care, and is thus dominant, in moderate and severe AD. Detailed appraisal again suggests that considerable caution is required in accepting this result with simple sensitivity analyses conducted by the report authors indicating incremental cost-effectiveness ratios (ICERs) which would not normally be considered cost-effective by NICE.

See section 6 for additional information about industry submissions.

PenTAG Cost–Utility Model

An in-depth consideration and exploration of various modelling approaches and limited availability of data led to the development of a decision model based broadly on the structure of the three-state Markov model described in the previous technology assessment report; based upon time to institutionalization, parameterised with updated estimates of effectiveness, costs and utilities. A review of all documentation (from manufacturers, interest groups, NICE and the published literature) relating to the decision model described in the previous Technology Assessment Report (TAR) was undertaken to develop a list of key criticisms or perceived weaknesses of the previous model. Using this list, a number of changes to the model structure and the parameter values used in the three-state Markov model were implemented. The model was developed in Microsoft Excel 2007 with additional analyses undertaken in the statistical software package R. A detailed description of the process undertaken to arrive at the PenTAG model can be found in Section 7.2 of the assessment report.

For the three cholinesterase inhibitors (where rivastigmine capsules were considered separately to rivastigmine patches), the base-case analysis modelled a cohort of people with mild to moderate AD. For memantine, the base-case analysis concerned people with moderate to severe AD. In exploratory sensitivity analyses, the cost-effectiveness of treatment with donepezil, rivastigmine (capsules and patches) and galantamine was investigated for a cohort of people with mild AD. Further exploratory sensitivity analyses investigated the cost–utility of donepezil, rivastigmine (capsules and patches), galantamine and memantine for people with moderate only AD and the cost-effectiveness of memantine in the treatment of people with severe only AD.

See section 7 for additional information on Assessment Group model.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Manufacturer's Model for Donepezil

The manufacturer of donepezil submitted an economic model that compared the cost effectiveness of donepezil with best supportive care in people with mild to moderate Alzheimer's disease using a discrete event simulation approach over a lifetime.

The manufacturer's base-case results estimated that donepezil dominated best supportive care because it was less costly and more effective in people with mild, moderate and mild to moderate Alzheimer's disease. The manufacturer reported per patient quality-adjusted life year (QALY) gains of 0.133 and 0.098 and estimated total per patient cost saving of £3379 and £1889 for groups with mild and moderate disease respectively.

Rivastigmine and Galantamine

The manufacturers of galantamine and rivastigmine did not submit new economic models.

Manufacturer's Model for Memantine

The manufacturer submitted a Markov cohort model of the cost effectiveness of memantine compared with best supportive care over a 5-year time horizon in people with moderate to severe Alzheimer's disease and a subgroup of people with aggression, agitation and/or psychotic symptoms at baseline based on the neuropsychiatric inventory (NPI) scale.

The manufacturer found that memantine dominated best supportive care (that is, no pharmacological treatment) because additional QALYs were gained (0.031) at a cost saving of £1711. Memantine treatment was associated with a delay to full-time care of 6 weeks. Additional treatment benefits were reported in the subgroup of patients with aggression, agitation and/or psychotic symptoms in whom the delay to full-time care was prolonged by up to 11 weeks with incremental QALY gains of 0.069 and a cost saving of £4971.

Assessment Group's Model - Subgroups of Mild, Moderate and Severe Alzheimer's Disease for All Treatments

The Assessment Group conducted analyses of the individual mild, moderate and severe populations for the acetylcholinesterase (AChE) inhibitors, AChE inhibitors and memantine, and memantine respectively (all including best supportive care). In the subgroup analyses for mild or moderate Alzheimer's disease, all treatments dominated best supportive care. Memantine had an incremental cost-effectiveness ratio (ICER) of £26,500 per QALY gained in severe disease.

Summary of the Appraisal Committee's Key Conclusions for Cost Effectiveness

The Committee considered that only the Assessment Group addressed the decision problem in the scope because it included all of the AChE inhibitors as comparators for mild to moderate Alzheimer's disease, whereas the manufacturer of donepezil's model compared donepezil with best supportive care only. The Committee concluded that although the Wolstenholme dataset that formed the basis of the Assessment Group's model had some limitations it still represented the best available data.

The Committee noted that the use of memantine in the subgroup with moderate disease would represent a cost-effective use of National Health Service (NHS) resources only if best supportive care was the comparator (that is, for people with moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors). The Committee concluded that treatment with memantine represented a cost-effective use of

NHS resources for people with severe Alzheimer's disease.

The Committee considered that, with the assumption that the key driver of cost effectiveness in the Assessment Group's model was treatment leading to delay to institutionalisation, the Assessment Group's model demonstrated that each of the AChE inhibitors was cost saving compared with best supportive care.

See sections 4.2 and 4.3 in the original guideline document for details of the economic analyses provided by the manufacturers, the Assessment Group comments, and the Appraisal Committee considerations.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated for each recommendation.

For clinical effectiveness, the Appraisal Committee considered evidence from the Assessment Group's review (17 new randomised controlled trials and four systematic reviews of randomised controlled trials), submissions from the manufacturers of donepezil, galantamine and memantine, the Alzheimer's Society, the Royal College of Psychiatrists, the British Geriatrics Society, clinical specialists and patient experts. For cost effectiveness, the Committee considered evidence from the Assessment Group's systematic review of economic evaluations, two cost-effectiveness models submitted by the manufacturers of donepezil and memantine, and the Assessment Group's independent economic model.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of donepezil, galantamine, rivastigmine and memantine for the treatment of patients with Alzheimer's disease

Potential Harms

- Common undesirable effects of donepezil include diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.
- Common undesirable effects of galantamine and rivastigmine are mainly gastrointestinal including nausea and vomiting.
- Common undesirable effects of memantine are dizziness, headache, constipation, somnolence and hypertension.

For full details of side effects and contraindications, see the Summaries of Product Characteristics.

Contraindications

Contraindications

For full details of side effects and contraindications, see the Summaries of Product Characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Clinical Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the National Health Service (NHS) in England and Wales on implementing National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on the NICE website (http://www.nice.org.uk/guidance/TA217).
    - Costing template and report to estimate the national and local savings and costs associated with implementation
    - Audit support for monitoring local practice

Implementation Tools

Audit Criteria/Indicators

Foreign Language Translations

Patient Resources

Quick Reference Guides/Physician Guides

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report

Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Mar. 84 p. (Technology appraisal guidance; no. 217).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2001 Jan (revised 2011 Mar)

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Professor Darren Ashcroft, Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester; Dr Brian Buckley, Lay member; Professor Usha Chakravarthy, Professor of Ophthalmology and Vision Sciences, The Queen's University of Belfast; Professor Peter Clark (*Chair*), Consultant Medical Oncologist, Clatterbridge Centre for Oncology; Dr Ian Davidson, Lecturer in Rehabilitation, The University of Manchester; Professor Simon Dixon, Senior Lecturer in Health Economics, University of Sheffield; Dr Alexander Dyker, Consultant Physician, Wolfson Unit of Clinical Pharmacology; Gillian Ells, Prescribing Advisor, NHS Sussex

Downs and Weald; Dr Jon Fear, Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds; Paula Ghaneh, Senior Lecturer and Honorary Consultant, University of Liverpool; Niru Goenka, Consultant Physician, Countess of Chester NHS Foundation Trust; Susan Griffin, Research Fellow, University of York; Professor Carol Haigh, Professor in Nursing, Manchester Metropolitan University; Alison Hawdale, Lay member; Professor John Hutton, Professor of Health Economics, University of York; Professor Peter Jones, Pro Vice Chancellor for Research & Enterprise, Keele University Professor of Statistics, Keele University; Dr Steven Julious, Senior Lecturer in Medical Statistics, University of Sheffield; Dr Vincent Kirkbride, Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield; Rachel Lewis, Doctoral Researcher; Dr Anne McCune, Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust; Professor Jonathan Michaels(*Vice Chair*), Professor of Vascular Surgery, University of Sheffield; Dr Neil Milner, General Medical Practitioner, Tramways Medical Centre; Professor Femi Oyebode, Professor of Psychiatry & Consultant Psychiatrist, The National Centre for Mental Health; Dr John Radford, Director of Public Health, Rotherham Primary Care Trust; Dr Phillip Rutledge, GP and Consultant in Medicines Management, NHS Lothian; Dr Stephen Saltissi, Consultant Cardiologist, Royal Liverpool University Hospital; Dr Brian Shine, Consultant Chemical Pathologist, John Radcliffe Hospital; Paddy Storrie, Lay member; Charles Waddicor, Chief Executive, NHS Berkshire; Dr Lok Yap, Consultant in Acute Medicine & Clinical Pharmacology, Whittington Hospitals NHS Trust

Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (amended). London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Aug 1. 84 p. (Technology appraisal guidance; no. 111).

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Mar. 2 p. (Technology appraisal 217). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .
- Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. Costing template and report. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Mar. (Technology appraisal 217). Available from the NICE Web site .
- Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. Audit support. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Mar. 10 p. (Technology appraisal 217). Available in Portable Document Format (PDF) from the NICE Web site .
- Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. Electronic audit tool. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Mar. Available from the NICE Web site .
- The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model. Peninsula Technology Assessment Group (PenTAG), University of Exeter; 2010 Jun 18. Electronic copies: Available in PDF from the NICE Web site .

Patient Resources

The following is available:

- Donepezil, galantamine, rivastigmine and memantine for Alzheimer's disease. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Mar. 4 p. (Technology appraisal 217). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site. Also available in Welsh from the NICE Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on February 16, 2007. It was updated in response to the September 2007 addendum on October 5, 2007, and again in response to the August 2009 addendum on December 4, 2009. This NGC summary was updated by ECRI Institute on November 9, 2011.

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